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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/564,579	05/10/2006	Daisuke Shii	06019/HG	2031

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EXAMINER	
EBRAHIM, NABILA G	

ART UNIT	PAPER NUMBER
1618	

MAIL DATE	DELIVERY MODE
04/02/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/564,579	SHII ET AL.	
	Examiner	Art Unit	
	NABILA G. EBRAHIM	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 December 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3,12 and 14-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3, 12, 14-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The receipt of Claims' amendments and Applicant's arguments dated 12/20/07 is acknowledged.

Status of claims: 3, 12, 14-18 are pending in the application.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 12, 14, and 15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claim recites a method for treating pruritus comprising a administering to a mammal 0.01 to 1% (w/v) of .. to the end of the claim. Neither the specification nor the original claims support this concentration, except for eye drops. Applicant is requested to show citation of this concentration in the original disclosure for other than eye drops. Note, the method claims are not limited to this means (e.g., eye drops) of adminstration. **This is a new matter rejection**.

Claim Rejections - 35 USC § 102

In light of the amendments to the claims, the rejection of claim 1-6, 8- 9, and 12-13 under 35 U.S.C. 102(b) as being anticipated by Nakai et al. WO 0214280 (hereinafter, the office action will use the corresponding document **EP1308440** as an English version) is herein withdrawn.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

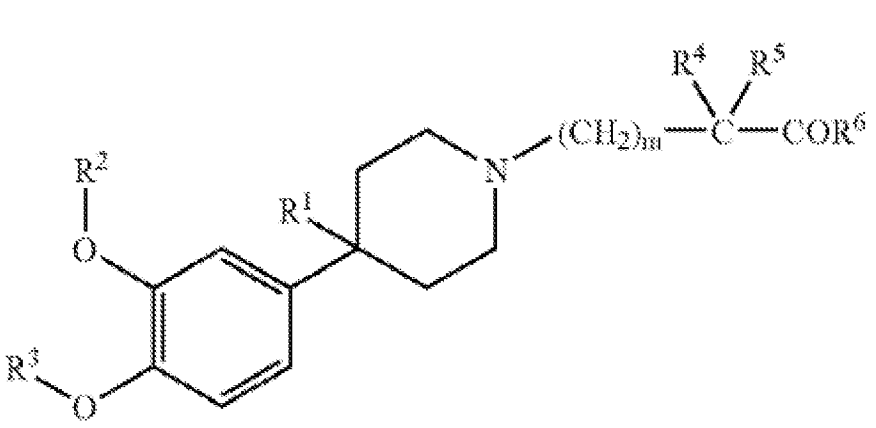
2. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

3. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 3, 12, 14-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nakai et al. WO 0214280 in view of Thomson et al. US 5756508 (Thomson) and further in view of Noyori et al. JP2002201126 (Noyori).

Nakai teaches the same compound as shown (see abstract, and page 4, lines 11+ for detailed description of the compound)



(I)

Nakai discloses that the agents which specifically inhibit PDE4 are useful in treating various diseases such as allergic diseases (e.g., allergic rhinitis, allergic conjunctivitis, seasonal conjunctivitis, atopic dermatitis, etc.), see page 2, lines 42+. Note that allergic rhinitis, allergic conjunctivitis, seasonal conjunctivitis cause eye pruritus as required by the instant claims. The compound represented by formula (I) may be administered in the form of liquid compositions such as eye lotion (page 27, lines 54+) and eye ointment (page 28, lines 29+).

Nakai also discloses that the dosages are determined depending on age, body weight, symptom, therapeutic effect, administration route, duration of the treatment and the like. Generally, 1 mg to 1000 mg per adult is orally administered once to several times per day (page 27, lines 48+).

Nakai is deficient in using the piperidine compound in eye drops.

Thomson teaches that in the vast majority of cases, treatment agents are administered to human eyes by the application of eye drops. Eye drops are typically made up at a concentration of active agent between about 0.1 and 4% in the ophthalmic medium. The reference also discloses that adjusting is expected to be acceptable as an

ophthalmic drop and practical in terms of known solubility and stability of piperidines (col. 6, lines 54+).

It would have been obvious to one of ordinary skill in the art to make dosage form in the form of eye drops using the compound disclosed by Nakai because Thompson teaches that piperidine eye drops has good stability and the reference also teaches that it has a good bioavailability (col. 3, lines 4+). It is also within the skill of an artisan to adjust the right dose as disclosed by Nakai (page 27, lines 48+).

Both references are deficient in disclosing a combination of piperidine and other drugs that treat eye allergy as require by claim 11.

Noyori teaches eye drops alleviating the unpleasant irritant eye ache at the time of instillation induced by sodium cromoglycate and enhancing the immediate antipruritic effects which an antihistaminic agent possesses to strongly suppress itchiness of the eyes immediately after the instillation is provided by formulating menthol to sodium cromoglycate and the antihistaminic agent.

Regarding the new claims, these are still properly rejected since Nakai discloses the use of the compound for allergic rhinitis, allergic conjunctivitis, seasonal conjunctivitis wherein all conditions cause eye pruritus. Further, Nakai teaches the use of an alkali metal hydroxide e.g., sodium hydroxide and a surfactants e.g., POLYSORBATE80 [0059]. Thompson also teaches that adjusting is expected to be acceptable as an ophthalmic drop and practical in terms of known solubility and stability of piperidines (col. 6, lines 54+).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine an antihistamine with the piperidine derivative in eye drops to relieve itching since it is known in the art that in most cases combining two drugs that have the same effect on a health problem would enhance their ultimate

effect. The skilled artisan would have good expectation of treating allergic itchy eyes by using eye drops ointment having piperidine derivative and another drug that have an anti-allergic effect.

Response to Arguments

1. Applicant's arguments filed 12/20/07 have been fully considered but they are not persuasive. Applicant argues that:

- Adjustment of the concentration of the active ingredient contained in an eye drop is generally determined in consideration of the physical properties, pharmacological effects and the like of the compound. The piperidine compound disclosed by Thompson and the compounds recited in applicants' present claims have only one chemical structure in common, which is the piperidine ring. Moreover, the main action of the compound of Thompson et al. and that of the compound recited in applicants' present claims are different from each other.

To respond: Thompson teaches clearly that eye drops are typically made up at a concentration of active agent between about 0.1 and 4% in the ophthalmic medium. This concentration overlaps with the concentration recited in the instant claims regardless of the function. Note that same compounds have same properties, if Thompson uses the compound as a muscarinic agonist in the eye, it would inherently work as PDE4 inhibitor as required by the instant claims. With regard to the dose needed to achieve the different effects, it is noted that since it is used for the same organ in the same way (topical), it is expected to be the same concentration. For example, using a tablet or two of acetyl salicylic acid (aspirin) would cause different effects such as analgesia control of body temperature, anti-inflammatory effect, and thinning of blood. Even if an eye problem would need a different concentration, it is within the abilities of a person of ordinary skill in the art to adjust the highest and lowest concentrations to be used.

- Thompson et al. have no teaching or suggestion for an eye drop concentration as low as 0.01% as recited in applicants' claims and as set forth in applicants' Examples. Such low eye drop concentration as claimed by the applicants provide an excellent antipruritic effect (see Table 1 on page ii of applicants' specification).

To respond: The concentration recited in the instant claims of 0.01 to 1.0% overlaps with the concentration disclosed by Thompson of 0.1 to 4.0%. Regarding table 1 in the instant specification, the table shows that a very low concentration of 0.01 has an effect on eye itching, however, the table also shows that a concentration of 0.1 gives a much better effect, accordingly, the more concentration included the better is the result in improving itching since the concentration is within the non-toxic or harmful amounts.

- According to the information provided in the drug package insert, TRAVATAN is a commercially available pharmaceutical product having a concentration of 0.004% which is lower than the range of concentration of the eye drop disclosed by Thompson et al.

To respond: The claim recites a range of 0.01 to 1.0% which overlaps with the disclosed concentration recited by Thompson.

- The eye drop at a concentration of 0.01 to 1% (w/v) is outside the range of the parenterally administered dosage disclosed by Nakai et al.

To respond: Nakai is relied upon for disclosing the compound which specifically inhibit PD recited in the instant claims. Further Nakai teaches the concentration in systemic therapeutic dosage forms other than eye drops such as tablets, capsules, etc. However, Nakai teaches that the compound can be comprised in eye lotions, a person of ordinary skill in the art would have been motivated to adjust the concentration in eye preparations such as eye drops since Nakai disclosure shows that the compound is safe to be used in eye preparations especially that Thompson teaches that adjusting is expected to be

acceptable as an ophthalmic drop and practical in terms of known solubility and stability of piperidines (col. 6, lines 54+).

- More specifically, the unit of concentration used in the present specification, w/v %, expresses the weight (g) of the active ingredient per i00 mL of solution. The maximum volume of an eye drop actually administered into an eye is considered to be at most 50 щL, since one drop of an eye drop generally contains 50 DL. Accordingly, when 1 mg/50 щL is expressed in w/v %, it is 2 g/100 mL, i.e., 2 w/v %. In contrast, 1 w/v %, which is the maximum dose for applicants' presently claimed eye drop, is calculated to contain 0.5 mg of active ingredient in a volume of 50 щL. Therefore, even the maximum dose of applicants' present claims (0.5 mg) is outside the range of the parenterally- administered dose disclosed in Nakai et al. (i to i00 mg).

To respond: again Nakai is relied upon for disclosing the compound which specifically inhibits PD recited in the instant claims. it is within the abilities of a skilled artisan to determine the optimum amounts to use and the optimum end points in using the compound. Note that Nakai teaches the concentration in a therapeutic dosage forms other than eye drops. However, Nakai teaches that the compound can be comprised in eye lotions, a person of ordinary skill in the art would have been motivated to adjust the concentration in eye preparations such as eye drops since Nakai disclosure shows that the compound is safe to be used in eye preparations especially that Thompson teaches that adjusting is expected to be acceptable as an ophthalmic drop and practical in terms of known solubility and stability of piperidines (col. 6, lines 54+).

- Applicant contends the combination of Nakai, and Thompson is unable to find that the concentration of 0.01 to 1% (W/V) is the optimal eye drop concentration of the recited in the instant claims.

To respond: Nakai teaches the agents which specifically inhibit PDE4 are useful in

treating various diseases such as allergic diseases, Thompson teaches that in the vast majority of cases, treatment agents are administered to human eyes by the application of eye drops. Eye drops are typically made up at a concentration of active agent between about 0.1 and 4% in the ophthalmic medium. It is noted that once a method of using a compound is known it is within the skill of the skilled artisan to determine the optimum amounts to use and the optimum end points in using the compound. It would have been obvious to try the exact concentration of the instant compound because a person of ordinary skill has good reason to pursue the known options within his technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense.

Conclusion

2. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nabila G. Ebrahim whose telephone number is 571-272-8151. The examiner can normally be reached on 8:00AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Nabila G Ebrahim/
Examiner, Art Unit 1618

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618